



Formulation and Characterization of Antioxidant Phytosome Gel of Kersen Leaves (*Muntingia calabura L.*)

Sandra Aulia Mardikasari¹, Nur illiyyin Akib², Suryani², Rezki Nahdiyati²

¹Faculty of Pharmacy, Hasanuddin University, 90245 Makassar, Indonesia; ²Faculty of Pharmacy, Haluoleo University, 93232 Kendari, Indonesia.

ABSTRACT

Introduction: Kersen leaves (*Muntingia calabura L.*) provide a great source of antioxidant activity, but have poor bioavailability through the skin. The use of Phytosome Delivery System was one of the strategies to increase the penetration to the skin.

Objective: This study aimed to develop the formula of Kersen leaves ethanol extract in Phytosome vesicles and to evaluate the stability of the phytosome Gel.

Method: Evaluation of phytosome gel stability was performed by cycling test includes observation of the organoleptic, pH, viscosity, spreadability, homogeneity, and the last was centrifugal tests to see the occurrence of phase separation of the gel.

Result: The results showed that phytosome of Kersen-leaves can be formulated in a gel dosage form with a concentration of Carbopol 940 at 0.5%, 1% and 1.5%. The formula of phytosome gel with gelling agent concentration 1% showed a good organoleptic, pH 6, the viscosity was 300 d.Pa.s, homogeneity, and there was no phase separation occurred after the centrifugal test.

Conclusion: This study provides an alternative method for utilizing antioxidant compounds from nature.

Key Words: Phytosome, Cycling test, Centrifugal test, *Muntingia calabura*

INTRODUCTION

Kersen (*Muntingia calabura L.*) is a plant that has potential as an antioxidant. Kersen leaves extract contains active components like flavonoids, saponins, and tannins which have the highest content when extracted using methanol and ethanol solvents.¹ Scientifically, it has been proven that Kersen leaves have a variety of pharmacological activities such as antioxidants, antiulcer, antipyretic, anti-inflammatory, anti-proliferative, and antibacterial.²

Flavonoids are natural antioxidants that can inhibit various reactions of oxidation, and reduce hydroxyl radicals, super-oxidation and peroxy radicals.³⁻⁵ But Flavonoids have a high polarity and these means have low bioavailability because it is difficult to penetrate the cell membrane. The problem that is often encountered in natural cosmetics preparations is stability and its ability to penetrate to the skin layer. The outermost layer of skin, the stratum corneum is a barrier to the absorption of percutaneous drugs, especially for polar compounds such as flavonoids. The use of a nano-sized carrier

system is one of the strategies that can be used to increase the penetration of compounds through the stratum corneum.⁶

One of the delivery system in transdermal delivery is Phytosomes. Phytosomes are a new form of herbal formulation that contains the chemically active component of the extract which is surrounded and bound by lipids. Phytosomes are a combination of phospholipids, that is phosphatidylcholine in nonpolar solvents.⁷ Polar herbal extracts absorbed by lipophilic Phytosomes in their outer layers show better absorption and as a result, produce better bioavailability and action than conventional herbal extracts in various dosage forms. To facilitate the application of the Phytosome, a gel formulation can be used. Gel preparation is widely used in cosmetics. The gel is preferred because the water content is quite large, gives a cold sensation to the skin, easily applied, and easily washed. But the problem that related to gel formulation is stability. Therefore this study aims to formulate the Phytosome of Kersen leaves ethanol extract into a gel form and to evaluate the stability of the phytosome gel preparation.

Corresponding Author:

Sandra Aulia Mardikasari, Faculty of Pharmacy, Hasanuddin University, 90245 Makassar, Indonesia.
Email: sandraaulia@unhas.ac.id

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MATERIALS AND METHODS

Materials

Kersen leaves ethanol extract (Kersen leaves samples were taken in Poasia Village, Poasia District, Kendari, Southeast Sulawesi), distilled water (Brataco), Ethanol 96% (Brataco), Carbopol 940 (Brataco), Triethanolamine (Brataco), Methylparaben (Brataco), Propylene glycol (Brataco) and Phosphatidylcholine (Sigma Aldrich).

Preparation of Phytosome Kersen Leaves Ethanol Extract

Phytosome was made using solvent evaporation and thin layer hydration methods. Phytosome suspension of ethanol extract of Kersen leaves was made in a volume of 50 mL with a comparison of the levels of the extract of Kersen leaves and phosphatidylcholine. The ratio used was 1.5% phospholipid and 1.5% extract which is the best ratio to produce Phytosome suspensions.⁸ Phosphatidylcholine was mixed into 10 mL of distilled water on a hot plate at 40°C and then dissolved in 10 mL of 96% ethanol to produce a mixture (a). The ethanol extract of Kersen leaves was dissolved in 10 mL 96% ethanol to produce a mixture (b). The mixture (b) was

added to the mixture (a) and stirred using a magnetic stirrer at a speed of 700 rpm for 5 minutes to form a mixture (c). Added 96% ethanol and continue stirring for 5 minutes at a speed of 700 rpm. Ethanol extract of Kersen leaves and phosphatidylcholine has been dissolved and then ultrasonicated for 30 minutes to obtain better solubility. The ethanol extract of the Kersen leaves and phosphatidylcholine from ultrasonication was poured in a round bottom flask, then the solvent was evaporated using a rotary evaporator with a rotation speed of 45 rpm at 40 ± 2°C until all the solvents were completely evaporated and a thin film was obtained. The thin layer was cooled and stored in a desiccator overnight to remove any remaining solvent residue. Hydration of the Phytosome thin layer using 20 mL distilled water using a rotary evaporator with a rotation speed of 90 rpm at 45°C for 20 minutes. Then the suspension obtained was transferred into the vial.⁹

Gel Formulation

The formula of Phytosome gel of Kersen leaves ethanol extract (*Muntingia calabura* L.), was made as much as 100 g containing ethanol extract by varying the composition of Carbopol 940 can be seen in Table 1.

Table 1: The formula of phytosome gel extract of Kersen leaves

Composition	Function	Formula % (b/v)		
		A	B	C
Phytosome of Kersen leaves ethanol extract (<i>Muntingia calabura</i> L.)	Active ingredients	1.5	1.5	1.5
Carbopol 940	Gel base	0.5	1	1.5
Triethanolamine	Gel stabilizer	1	1	1
Propylene glycol	Humectant	10	10	10
Methylparaben	Preservatives	0.09	0.09	0.09
Vanilla essence	Flavour	q.s.	q.s.	q.s.
Aquades	Solvent	ad 100	ad 100	ad 100

The gel base (Carbopol 940) was developed separately with distilled water approximately twenty times the weight of Carbopol 940. The base was allowed to stand for ± 20 minutes then stirred and added a neutralizing base, TEA, into the gel base.⁶ After the gel base was formed, Phytosome suspension of Kersen leaves ethanol extract was added and stirred until homogeneous, then methylparaben is added which has been dissolved before in a portion of propylene glycol and all stirred until homogeneous.¹⁰

Cycling test

The cycling test method is one of many ways to evaluate the stability of a pharmaceutical preparation. This method consists of one cycle of gel preparations stored at 4°C for 24 hours then removed and placed at ± 40°C for 24 hours. This

experiment was repeated in 6 cycles. The physical condition of the gel was compared during the experiment with previous preparations.¹¹

a. Organoleptic Observation

Organoleptic observation can be assessed from the texture of the preparation including changes in colour and odour of the gel. Observations were made on newly made and stored gels¹². Stable gels must exhibit the same character in the same colour and odour before and after accelerated storage conditions.¹³

b. Gel pH Test

Universal pH indicator paper is inserted into the gel and then matched with the pH indicator colour printed on the container.¹⁴

c. Viscosity Test

The viscosity of the formulation was determined by Rion Rotor Viscotester VT-04 using spindle no. 3. The gel is put into the beaker, then the spindle is dipped in the gel not to touch the container. Then the viscometer is turned on and seen on what scale the viscometer is designated.¹⁵

d. Gel Spreadability

Weighed 1 gram of gel and placed it in the middle of a round glass. Before weighing the other glass first and place the glass on the gel and leave it for 1 minute, then measure the diameter of the gel that spreads by taking the average length of the diameters from several sides. The amount of load added is 100 grams with the addition of each load as much as 50 grams. Leave the gel for 1 minute, then note the diameter of the gel on four sides and determine the spread area of the gel.¹⁶

e. Homogeneity Test

Homogeneity checks were carried out using glass objects where several gel preparations were applied to a piece of glass or other suitable transparent material, preparations must show a homogeneous arrangement and no coarse grains are seen.¹⁶

f. Centrifugal test

Gel sample is centrifuged at a speed of 6000 rpm for 30 minutes then the physical changes are observed.¹⁷

RESULTS AND DISCUSSIONS

Phytosome of Kersen Leaves Ethanol Extract

Natural substances such as flavonoids have good solubility in water because they are polar, but they are difficult to absorb because of their large size and poor solubility in lipids. As a result, the ability of flavonoids to penetrate the outer membrane which is rich in lipids is very limited. Polar natural materials such as flavonoids can be transformed into complex molecules so that they can be mixed with lipids called Phytosomes. Phytosomes are a drug delivery system consist of polyphenol compounds found in plant extracts that are bound directly to phosphatidylcholine. Phytosomes are used to deliver active substances that have poor penetrating skin properties.³ In this research, the preparation of ethanol extract of Kersen leaves in the vesicular carrier of Phytosome was done, with the Phytosome constituent materials are phosphatidylcholine, ethanol, and water. Phytosomes vesicular carriers in this study were made using mechanical dispersion methods and solvent evaporation. The material used is phosphatidylcholine derived from the phospholipid group which is dispersed in an ethanol solvent known as phytochromes. In the formation of phytosome complexes, the ratio of this ratio between flavonoids and phospholipids

ranges from 0.5-2 mol. The most preferred ratio of phospholipids is the 1:1 ratio between flavonoids and phospholipids.⁸

Phosphatidylcholine was used because it was a phospholipid that commonly found in cell membranes, so vesicles that resemble biological membranes can be produced. Phosphatidylcholine is the most widely used because it was made from natural ingredients, membranes that form resemble cell membrane lipids and are biocompatible (biodegradation, nontoxic, and do not trigger an immune response). Phosphatidylcholine was also stable and safe.⁷ Phosphatidylcholine functions as a vesicle maker by forming a double lipid layer. The use of phosphatidylcholine must not be too low and should not be too high, because if the concentration is too low then only small vesicles are formed and if the concentration of phosphatidylcholine is too high it will make the vesicles too soft which can cause leakage in the vesicles and will eventually reduce the value of absorption efficiency.⁸

Ethanol was a solvent used in phytosome preparations. Besides being used as a solvent, ethanol can also function as an enhancer of penetration into the skin. Also, ethanol will affect vesicles by making the vesicle structure less dense so that active substances easily enter the lipid bilayer. Water was also needed in the process of preparation of phytosome vesicles. According to Kalita, et al., 2013, phytosome vesicles are formed when phosphatidylcholine is dispersed into water, then it will automatically form a closed spherical vesicle.¹⁸ The phospholipid will bend to reduce the angle of contact with the aqueous medium until finally the two ends of the phospholipid meet and form a closed, rounded space. When vesicles are combined with alcohol, they form softer structures that have good stability and increase the ability of vesicles to penetrate into the stratum corneum.



Figure 1: Phytosome Suspension.

The formula is prepared by the method of solvent evaporation and thin layer hydration. Before the sonication process, the Phytosome suspension formed is faded yellow and smells typical of a mixture of Kersen leaves and ethanol extracts, while after the sonication process the Phytosome suspension

formed appears more transparent as shown in Figure 1. This is due to the size of the vesicles formed after the sonication process becomes smaller because of the presence of ultra-sonic sound vibrational energy that breaks the structure of vesicles and separates attached vesicles so that the Phytosome more transparent. Based on the results of the characterization of Phytosome vesicles, formulas with a variation ratio of 1.5% extract and 1.5% phosphatidylcholine have an absorption efficiency value of 68.80%, Phytosome particle size distribution of 419.6 nm and have vesicle morphology that is large single layer vesicles or Large Unilamellar Vesicle (LUV).

Preparation of Phytosome Gel

The gel formula used in this study was Phytosome suspension of ethanol extract of Kersen leaves as an active substance, Carbopol 940 as a gel base with different concentration variations of 0.5% (FI), 1% (FII) and 1.5% (FIII) as a gelling agent, triethanolamine as a base stabilizer, propylene glycol as a humectant, methylparaben as a preservative and aqua dest as a carrier (Figure 2).

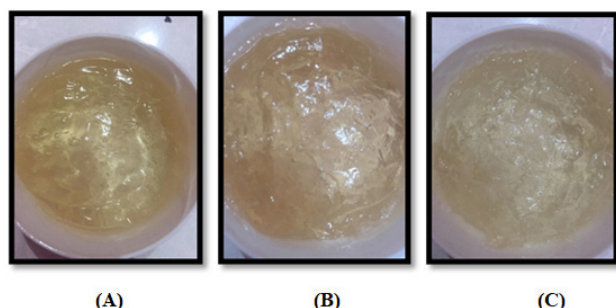


Figure 2: Phytosome Gel Formulation.

The process of developing Carbopol by using triethanolamine, Carbopol expands into a clear rigid gel. This process occurs because carbopol is an anionic polymer which is free acid and carbopol water media is initially uniformly dispersed then the gel is neutralized with a base so there is a gap of negative charge along the polymer chain and causes the polymer to decompose and then expand to form semi-solid preparations and become slightly rigid.

One of the disadvantages of gel is that it hardens quickly when exposed to open air for a relatively long time. This hardness or stiffness is caused by evaporation of water from the base of the preparation, to overcome this situation is done by adding humectants.¹⁹ Humectants are added to prevent the preparation from drying out and losing large amounts of water. A thin humectant layer will form to retain moisture and prevent dry skin.²⁰ Humectants used in this study were propylene glycol. Propylene glycol is used as a humectant that will maintain the water content in the preparation so that the physical properties and stability of the preparation during

storage can be maintained. Propylene glycol has good stability at pH 3-6.²¹

High water content in the gel preparation will cause easy microorganisms or fungi that grow, therefore in the manufacture of gels, it is necessary to add preservatives. The preservative used is methylparaben. The advantage of methylparaben is that it has a wide spectrum of Gram-positive and Gram-negative bacteria, fungi, low toxicity and stability over a wide pH range.²²

Cycling test

The stability of a substance is something that needs to be considered in making pharmaceutical preparations. This is important because preparation is usually produced in large quantities and requires a long time to reach the hands of consumers. Therefore these preparations need to be tested for stability with established procedures.²³ The stability test used in this study is the Cycling test and centrifugal test. Cycling test aims to see the resistance of the preparation to changes in temperature. This test is carried out on preparations with different storage temperatures ie starting at 4°C for 24 hours then continuing to store at 40°C for 24 hours (1 cycle). Tests carried out as many as 6 cycles or 12 days. The gel test results before and after the Cycling test (appendix 11) can be seen visually without syneresis, indicating there is no phase separation in the gel before and after the Cycling test. This indicates that the gel does not experience inter-cell fluid discharge which causes the gel to contract. also besides, the gel stability test is carried out by organoleptic test, pH test, viscosity test, test, homogeneity and diffusion test.²⁴

a. Organoleptic Observation

Organoleptic observation aims to see the physical appearance of a preparation which includes shape, colour and odour. Organoleptic observations were carried out to determine which gels were made following the colour and odour of the phytosomes used. Organoleptic observations can be seen in the following Table 2:

Table 2: Organoleptic characteristics of gel before and after the cycling test

Formula	Shape		Colour		Odour	
	Before	after	before	after	before	after
A	not sticky	not sticky	Yellow	Yellow	Vanilla scent	Vanilla scent
B	not sticky	not sticky	Yellow	Yellow	Vanilla scent	Vanilla scent
C	not ticky	not sticky	Faded yellow	Faded yellow	Vanilla scent	Vanilla scent

Formula A: 0.5% carbopol concentration;

Formula B: 1% carbopol concentration;

Formula C: 1.5% carbopol concentration

Organoleptic observations showed that the phytosome gel of the Kersen leaves ethanol extract showed no phase separation, this is because the active substance and gel base were homogeneously mixed and the amount of gelling agent was sufficient to stabilize the gel. Thus indicating that the gel with various base concentrations is physically stable in an accelerated storage time (Cycling test).

b. pH test

The pH test of the preparation is a physicochemical parameter that must be performed on the dermal preparation because the pH of the preparation can affect the effectiveness, stability, and comfort of the use of the preparation on the skin when used.¹⁹ The pH of preparation depends on the constituent components of either the active substance or the additives used in the formulation. The pH that is too acidic or basic can cause the skin to become dry and irritated due to damage to the acid mantle in the stratum corneum layer.²⁵ The results of pH testing of Dalat gel preparations are seen in Table 3 below:

Table 3: Results of pH of Phytosome gel preparations

Formula	pH	
	before cycling test	after cycling test
A	9	9
B	6	6
C	6	5

The results obtained from the measurement of pH in gel preparations with the determination of the pH value of cosmetic preparations is from 4.5 to 6.5.²⁶ The difference in the concentration of the gel base can affect the pH value of the gel preparations can be seen in the table, the measurement results of the gel obtained pH that increases with the increase in the concentration of the gel base used. This is because carbopol has an acidic pH of 2.3 so that an increase in the concentration of the gel base will increase the pH value of the preparation. The results obtained indicate that the Phytosome gel formula is safe to use on the skin.

c. Viscosity Test

Viscosity measurements are important because they affect the convenience of use and stability of a preparation. Viscosity is the resistance of a liquid that flows, the value of viscosity is directly proportional to the resistance. The higher the concentration of carbopol can increase the viscosity of the gel, in general, the increase in viscosity can increase the stability of the preparation (based on the law of Stokes).²⁷ Viscosity test results can be seen in the following Table 4:

Table 4: Results of the gel preparation viscosity

Formula	Gel Viscosity (d.Pa.s)	
	before cycling test	after cycling test
A	110	100
B	370	300
C	400	380

The results of the gel viscosity test showed that increasing the concentration of the gel base in the preparation the higher the value of the viscosity of the preparation. The decrease in gel viscosity after the Cycling test is caused by high temperatures increasing the distance between particles so that the force between particles will decrease. Increasing distances cause viscosity to decrease.²⁸ Also, this can be caused by the humidity in the storage room and packaging that is less impermeable, so that it can cause the gel to absorb water from outside. The viscosity value obtained is still within the range of 50 d.Pa.s to 400 d.Pa.s so that the gel preparation is stable.²⁹ Viscosity of the dosage must not be too high or too low, because the viscosity is too high will make the gel thicker resulting in more difficult drugs regardless of the gel preparation, while too low viscosity will reduce the length of time the gel stays in the skin.³⁰

d. Homogeneity Test

A homogeneity test was done to investigate whether the preparations that have been made are homogeneous or not. Homogeneity test was obtained by applying a gel sample to a piece of glass or other transparent material. The preparation must show a homogeneous arrangement and no coarse grains are seen. Homogeneity test results can be seen in the following Table 5:

Table 5: Homogeneity test before and after the cycling test

Formula	Before cycling test	After cycling test
A	Homogeneous, no coarse grain	Homogeneous, no coarse grain
B	Homogeneous, no coarse grain	Homogeneous, no coarse grain
C	Homogeneous, no coarse grain	Homogeneous, no coarse grain

The results of observing the homogeneity of phytosome gel preparations in formulas I, II, and III have good homogeneity. Where homogeneity affects the effectiveness of therapy because it is associated with the same drug levels in each use.²⁷

e. Spreadability Test

The spreadability test is related to the gel dispersion properties when used in topical preparations. The greater the spread power, the surface area of the skin in contact with the gel will be more extensive and the active substance will be well absorbed.²⁷ Dispersibility is an important characteristic in formulations because it affects the transfer of active ingredients to the target area in the right dosage, ease of use, the pressure needed to get out of the package, and acceptance by consumers.²⁹ The spread test results can be seen in Table 6.

Table 6: Spreadability tests before and after the cycling test

Formula	Diameter (cm)	
	before cycling test	after cycling test
A	3.17	4.73
B	3.85	4.80
C	3.65	4.35

Based on the test results above, it can be seen that the gel dispersion does not match with the requirements of the semi-solid dispersion parameters, namely 5-7 cm.²⁹ The spreadability of the gel is not too large due to several kinds of factors such as viscosity and gel base characteristics. The spreadability is influenced by viscosity, where the spread power has an inverse relationship with viscosity that is the greater the value of viscosity, the value of the spreadability is smaller and the smaller the viscosity value, the value of the spreadability is also greater. Also, if the applied pressure is the same for each gel formula test, the thicker the preparation of the spreadability will be smaller.¹⁶

f. Centrifugal test

Centrifugal test or mechanical test is one of the gel stability tests by looking at the mechanical effect on phase separation. Centrifugal tests were carried out on all newly made phytosome gel formulas. Tests carried out using a centrifuge at a speed of 6000 rpm for 30 minutes. According to Elya, B (2013), the mechanical influence gives an idea of the magnitude of the influence of the gravitational force on gel storage for one year.³¹ Centrifugal test observations can be seen in figure 3.

The observations showed no phase separation in all gel formulas. The stability of gel preparation is related to the shelf life of the gel.³² The results obtained indicate that the gel preparation has a shelf life for one year. This result is caused by no phase separation after being given the effect of the centrifugal force exerted by the centrifugation

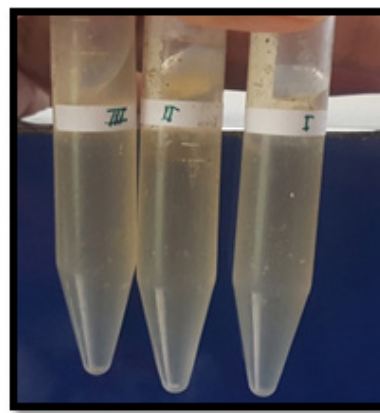


Figure 3: Centrifugal test results of phytosome gel preparations.

CONCLUSION

Based on the results of the research that has been described previously it can be concluded that Kersen leaves phytosomes can be formulated in the form of gel preparations with carbopol 940 concentrations of 0.5% 1% and 1.5%. The formulation of Kersen leaves phytosome gel has good stability in formula B in terms of organoleptic parameters with the consistency of thick, yellow-coloured, Vanilla-scented, pH 6, viscosity 100 d.Pa.s-300 d.Pa.s, homogeneous, and no phase separation occurs. However, the results obtained in the spreadability do not match the requirements.

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